UTILITY OF TRANSRECTAL ULTRASOUND WITH POWER DOPPLER IMAGING GUIDED BIOPSY IN THE DETECTION OF PROSTATE CANCER

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DECLARATION

I solemnly declare that this dissertation titled "**Utility of Trans Rectal Ultrasound with Power Doppler Imaging guided biopsy in the detection of prostate cancer**" was prepared by me in the Department of Urology, Government General Hospital, Chennai under the guidance and supervision of **Prof. R. Jeyaraman, M.Ch .,** Professor & Head of the Department, Department of urology, Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of M.Ch. Urology.

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CONTENTS

INTRODUCTION

Prostate cancer is the most common noncutaneous cancer among males.[1] It accounts for 10% of cancer related deaths in males. According to the American Cancer Society, 186330 new cases will be diagnosed in 2008 and 26000 men will die from prostate cancer[1]. Prostate cancer is rarely diagnosed in men younger than 40 years, and it is uncommon in men younger than 50 years. Prostate cancer is also found during autopsies performed following other causes of death. The rate of this latent or autopsy cancer is much greater than that of clinical cancer. In fact, it may be as high as 80% by age 80 years. [2]

The diagnosis and treatment of prostate cancer continues to evolve. With the development of prostate-specific antigen (PSA) screening and TRUS, prostate cancer is being diagnosed earlier in the disease course.

In the present era, most patients present because of abnormalities in Prostate Specific Antigen (PSA) level or positive digital rectal examination (DRE) findings while evaluating for BPH, rather than metastatic symptoms. The combination of DRE and serum PSA is the most useful first-line test for assessing the presence of prostate cancer in an individual.[3] However, prostate cancer can be an incidental pathologic finding when tissue is removed during transurethral resection to manage obstructive prostatic symptoms.

The presence of prostate disease (prostate cancer, BPH, and prostatitis) is the

most important factor affecting serum levels of PSA.[4,5,6]. PSA elevations may indicate the presence of prostate disease, but not all men with prostate disease have elevated PSA levels. Furthermore, PSA elevations are not specific for cancer.

Findings from the DRE are crucial. An irregular firm prostate or nodule is typical, but many cancers are found in prostates that feel normal. DRE is a test with only fair reproducibility even in the hands of experienced examiners that misses a substantial proportion of cancers. [7, 8, 9] DRE detects most cancers at an advanced pathologic stage, when treatment is less likely to be effective. DRE misses 23% to 45% of the cancers that are subsequently found with prostatic biopsies done for serum PSA elevations. [7]

A number of studies have confirmed the inability of TRUS to localise early prostate cancer. [10, 11, 12] Rifkin and colleagues[10] found that only 60% of prostate cancers measuring more than 5 mm on pathologic examination were identified by MRI and that ultrasonography identified only 59% of these cancers. Flanigan and associates[12] found that only 18% of 855 sonographically suspicious quadrants actually contained cancer on biopsy, whereas 65% of quadrants containing cancer were not sonographically suspicious. Any patient with a DRE suspicious for cancer or a PSA elevation should undergo prostate biopsy regardless of TRUS findings if an early diagnosis of cancer would result in a recommendation for treatment.

The original sextant biopsy scheme (one core from the base, mid, and apex bilaterally) significantly improved cancer detection, over digitally directed biopsy of

palpable nodules and TRUS guided biopsy of specific hypoechoic lesions. Presti and co-workers found that adding laterally directed cores from the base and midgland bilaterally improved cancer detection from 80% with standard sextant to 96%.[13]

To improve the detection rate with TRUS biopsy various additional modalities have been tried. This includes power Doppler ultrasonography to evaluate the neovascularity in patients with prostate cancer. Various studies have shown increased cancer detection rates using Doppler-targeted biopsy strategies.[14,15,16,17] To evaluate the Indian perspective regarding the Doppler directed targeted biopsy strategies, we decided to conduct a study to evaluate the utility of power Doppler ultrasonography in the detection of prostate cancer.

AIM

To evaluate the utility of trans rectal ultrasound with power Doppler imaging guided biopsy in comparison with grey scale imaging in the detection of prostate cancer, 10 core biopsy being the reference standard.

REVIEW OF LITERATURE

Prostate cancer is the fourth most common male malignant neoplasm worldwide.[18] Prostate cancer has been the most common visceral malignant neoplasm in U.S. men since 1984, now accounting for one third of all such cancers [1]. 10% of cancer-related death in males is caused by prostate cancer[1] The incidence of prostate cancer peaked in 1992, approximately 5 years after introduction of prostate-specific antigen (PSA) as a screening test; it fell precipitously until 1995 and has been rising slowly since then, at a slope similar to that observed before the PSA era. [19]

According to figures from the American Cancer Society, 186,330 new cases will be diagnosed in 2008 and 26,000 men will die from prostate cancer. Prostate cancer is uncommon in men younger than 50 years. [20] Prostate cancer is also found during autopsies performed following other causes of death. The rate of this latent or autopsy cancer is much greater than that of clinical cancer. In fact, it may be as high as 80% by age 80 years. [1]

The lifetime risk (from age 0 to 90 years) of death from prostate cancer is 3% and the lifetime risk of a diagnosis of prostate cancer is 17% [21]

Anatomy and Internal Structure of the Prostate Gland

Overview of Prostate Anatomy

The adult prostate is a chestnut-shaped organ enveloped in a fibrous capsule. The base of the prostate is attached to the bladder neck, and the apex is fixed to the urogenital diaphragm. The prostatic urethra traverses the gland. The verumontanum is a longitudinal ridge in the prostatic apex on which the ejaculatory ducts open. The prostate is related superiorly and posteriorly to the seminal vesicles. The ampullae of the vas deferens run medial to the seminal vesicles along the posterior surface of the prostate. Anteriorly, the fibrous capsule thickens at the level of the apex to form the puboprostatic ligaments, which attach the prostate to the back of the symphysis pubis. The dorsal venous complex (i.e. Santorini's plexus) runs along the puboprostatic ligaments. The prostate gland lies beneath the endopelvic fascia. Posteriorly, the 2 layers of Denonvillier's fascia separate the prostate from the rectum. The rectourethralis muscle attaches the rectum to the prostatic apex.

A rich plexus of veins encompasses the prostate gland between the true fibrous capsule of the gland and the lateral prostatic fascia; these are visible landmarks on sonograms. The neurovascular bundles run craniocaudally along the posterolateral aspects of the prostate. The prostate gland is supplied by the prostatic artery, which is usually a branch of the inferior vesical artery. The prostatic artery is divided into an urethral branch, which supplies the adenoma, and a capsular branch. Venous drainage

from the prostate moves into the Santorini's plexus and eventually into the internal iliac vein. The prostatic venous plexus communicates freely with the extradural venous plexus (i.e., Batson plexus), which is thought to be factor in the spread of prostate cancer. Initially, lymphatic drainage of the prostate is into the obturator lymph nodes and into the hypogastric chain.

The nerve supply to the prostate is both sympathetic, from the hypogastric plexus (L1-2), and parasympathetic, from the pelvic nerve (nervi erigentes (S2-S4). Although the cavernous nerves run along the posterior aspect of the prostate, the 2 distinct areas from which prostatic nerves leave the gland are thought to be the superior and inferior pedicles. These areas are the first sites of extraprostatic spread of cancer.

Internal Architecture and Anatomy of the Prostate

According to the classic work by McNeal, the prostatic urethra, which is the main reference point of the prostate, divides the gland into an anterior fibromuscular stroma and a posterior glandular organ. The urethra angulates 35° anteriorly in the proximal portion of the prostate. The ejaculatory ducts run in the same plane as the distal prostatic urethra to join the verumontanum. Lowsley's concept of a 5-lobed prostate has been replaced by McNeal's concept of zonal architecture. The prostate has 4 glandular zones, each with their own ductal system. The peripheral zone, transition zone, and periurethral glands have similar histological appearance and are derived from the urogenital sinus. However, the central zone is histologically distinct and is derived from mesonephric

tissues (i.e., wolffian tissue).

Peripheral zone

The peripheral zone constitutes almost 75% of the normal prostate gland. It occupies the distal prostate gland, the area around the urethra distal to the verumontanum. Their ducts drain distal to the verumontanum. Approximately 70% of carcinoma of the prostate (CAP) arise in this zone.

Central zone

The central zone constitutes 25% of the normal prostate and occupies the part of the prostate behind the proximal prostatic urethra. The ejaculatory ducts traverse through the central zone. Approximately 5-10% of CAP arise in this zone.

Transition zone

The transition zone makes up approximately 5-10% of the normal prostate gland. The transition zone lies on either side of the proximal prostatic urethra lateral to the internal sphincter. Approximately 20% of CAP cases arise in the transition zone.

Periurethral glands

The periurethral glands comprise less than 1% of the glandular tissue. **Anterior fibromuscular stroma**

The anterior part of the prostate is composed mainly of fibromuscular stroma, which is continuous with detrusor fibres. Toward the apex of the gland, this fibromuscular tissue blends with striated muscle from the levator. Puboprostatic ligaments also blend with this area.

Invaginated extraprostatic space

As the ejaculatory ducts enter the prostate posteriorly, an invaginated extraprostatic space (IES) surrounds them and invaginates into the prostate. The IES surrounds the ejaculatory ducts, ends at the verumontanum, and communicates with the periurethral space. In 1989, Lee first introduced the concept that invasion of the IES may be the first sign of extraprostatic extension of prostate cancer and an early sign of invasion of seminal vesicles[22]. In 2005, Amin et al evaluated the pathological significance of the invasion of IES in 80 patients with prostate cancer and concluded that IES involvement was consistently seen in cases with seminal vesicle invasion.[23]

Bladder neck and the internal sphincter

The internal sphincter runs from the bladder neck to the level of the verumontanum. The smooth muscle fibres of the sphincter are continuous with the superficial layer of the trigone. In healthy males, the bladder neck and the internal sphincter are closed. In males with a neurogenic bladder, the bladder neck and the prostatic urethra are wide open, and some investigators have used transrectal

ultrasonography (TRUS) to monitor the lower urinary tract in patients with spinal injuries.

Pathophysiology and Natural History of prostate cancer[25]

Pathophysiology

Prostate cancer develops when the rates of cell division and cell death are no longer equal, leading to uncontrolled tumour growth. Following the initial transformation event, further mutations of a multitude of genes, including the genes for p53 and retinoblastoma, can lead to tumour progression and metastasis. Most (95%) prostate cancers are adenocarcinomas arising from the prostatic gland acini.

Approximately 4% of cases of prostate cancer have transitional cell morphology and are thought to arise from the urothelial lining of the prostatic urethra. Few cases have neuroendocrine morphology. When present, they are believed to arise from the neuroendocrine stem cells normally present in the prostate or from aberrant differentiation programs during cell transformation.

Of prostate cancer cases, 70% arise in the peripheral zone, 15-20% arise in the central zone, and 10-15% arise in the transitional zone. Most prostate cancers are multifocal, with synchronous involvement of multiple zones of the prostate, which may be due to clonal and nonclonal tumours.

Natural history

The natural history is still relatively unknown, and many aspects of progression are poorly understood. Symptoms or abnormal DRE findings in the pre-PSA era brought only 40-50% of patients with prostate cancer to medical attention, and these patients usually had locally advanced disease. The advent of PSA testing has helped to identify patients with less-advanced, organ-confined disease.

In fact, the pendulum has shifted to the point that certain members of the urologic community feel that active surveillance, also known as expectant management, may have a role. Twenty-year outcome data from Connecticut confirm that mortality rates due to tumours with a Gleason score of 2-4 was less than 7%.[25] Urologists at Johns Hopkins University advocate active surveillance in patients with a PSA density of less than 0.1 ng/mL, with no adverse pathologic findings on needle biopsy, and with tumours with a Gleason score of 6 that are smaller than 3 mm.

Evidence suggests that most prostate cancers are multifocal and heterogeneous. Cancers can start in the transitional zone or, more commonly, the peripheral zone. When these cancers are locally invasive, the transitional-zone tumours spread to the bladder neck, while the peripheral-zone tumours extend into the ejaculatory ducts and seminal vesicles. Penetration through the prostatic capsule and along the perineural or vascular spaces occurs relatively late.

The mechanism for distant metastasis is poorly understood. The cancer spreads to bone early, occasionally without significant lymphadenopathy. Currently, 2 predominant

theories have been proposed for spread—the mechanical theory and the seed-and-soil theory. The mechanical theory involves direct spread through the lymphatics and venous spaces into the lower lumbar spine. Advocates of the seed-and-soil theory believe that tissue factors that allow for preferential growth in certain tissues, such as the bone, must be present. Lung, liver, and adrenal metastases have also been documented. Specific tissue growth factors and extracellular matrices are possible examples.

The doubling time in early-stage disease is as slow as 2-4 years, but this changes as the tumour grows and becomes more aggressive. Larger tumours usually have a higher Gleason grade and a faster doubling time.

Natural history by stage

T1a - Progression over 10 years (uncommon)

T1b - Tumour-related death rate of 10% in 10 years

T2 - Ten-year metastasis-free survival rate of 81% with grade 1, 58% with grade 2, and 26% with grade 3

T3 - Lymph node metastasis at presentation in 50% and approximately 25% rate of 10-year disease-free survival

The natural history of clinically localized disease varies, with lower-grade tumours having a more indolent course, while some high-grade lesions progress to metastatic disease with relative rapidity. Several studies have examined the cancer-specific and quality-of-life outcomes associated with a watchful-waiting approach to

localized disease. Albertsen et al monitored patients who received no initial treatment for prostate cancer.[25] As disease progression occurred, many received anti-androgens. Men with poorly differentiated tumours lost 6-8 years of life, while those with moderately differentiated tumours lost 4-5 years. Of all men monitored for 10 years, 40% died of causes other than prostate cancer. This study was performed prior to PSA screening.

Graversen et al compared watchful waiting with radical prostatectomy.[26] They found no overall difference in survival, but they did find that a high Gleason score was associated with poor survival in both groups. Chodak et al confirmed this finding by analyzing 6 studies and finding a 34% survival rate associated with grade 3 tumours versus an 87% disease-specific survival rate associated with grade 1 and 2 tumors.[27] The metastasis-free survival rate also significantly dropped as the grade progressed from 1 to 3.

Johansson et al (2004) reported their recent update on a population-based cohort study with a mean observation period of 21 years[28]. Prostate cancer specific mortality increased from 15 deaths per 1000 person-years during the first 15 years to 44 deaths per 1000 person-years beyond 15 years of follow-up.

Taken together, these data suggest that, although most prostate cancers diagnosed at an early stage have an indolent course, local tumour progression and aggressive

metastatic disease may develop in the long term. In addition, these findings would support early radical treatment, notably among patients with an estimated life expectancy exceeding 15 years.

Detection of prostate cancer

The histologic diagnosis of prostate cancer is made, in the majority of cases, by prostate needle biopsy. Prostate cancer rarely causes symptoms until it is advanced. Although there is controversy regarding the benefits of early diagnosis, it has been demonstrated that an early diagnosis of prostate cancer is best achieved using a combination of DRE and PSA. Transrectal ultrasound (TRUS)-guided, systematic needle biopsy is the most reliable method, at present, to ensure accurate sampling of prostatic tissue in men considered at high risk for harbouring prostatic cancer on the basis of DRE and PSA findings.

The presence of systemic symptoms (e.g., bone pain, renal failure, anaemia) as a result of prostate cancer suggests locally advanced or widely metastatic disease. Growth of prostate cancer into the urethra or bladder neck can result in obstructive (e.g., hesitancy, decreased force of stream, intermittency) and irritative (e.g., frequency, nocturia, urgency, urge incontinence) voiding symptoms. Impotence can be a manifestation of prostate cancer that has spread outside the prostatic capsule to involve the branches of the pelvic plexus (neurovascular bundle)

The routine use of DRE and PSA testing in asymptomatic men as a means of reducing prostate cancer mortality by earlier detection and treatment remains controversial [29, 30].

The U.S. Preventive Services Task Force concluded that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA testing or DRE. The American Cancer Society [20] and the American Urological Association recommended that prostate cancer screening with PSA and DRE be offered to all men older than 50 years and that the risks and benefits of screening be discussed with the patient.

The PLCO trial was designed to address whether or not screening reduced prostate cancer mortality given the practices of diagnosis and treatment in the community. Follow-up biopsies for a positive screen and specific treatments for prostate cancer are not mandated in this trial. Pinsky et al reported low follow-up biopsy rates after a positive screen in the PLCO trial, and whether this will compromise the ability of the trial to demonstrate a screening effect is controversial. [31] The PLCO has a calculated power of 90% to show a mortality reduction of 20% in the screened population if the compliance rate is 90% and the contamination rate is 20% [32]

In the ERSPC, recruitment of 165,000 men to the core age group of 55 to 69 years will have a power of 86% to show a 20% to 25% mortality reduction in 2008 if the

contamination rate is 20% [32]

Digital Rectal Examination

Before the availability of PSA testing, physicians relied solely on DRE for early detection of prostate cancer. DRE is a test with only fair reproducibility even in the hands of experienced examiners that misses a substantial proportion of cancers and detects most cancers at a more advanced pathologic stage, when treatment is less likely to be effective. [9] In both screened and unscreened populations, DRE misses 23% to 45% of the cancers that are subsequently found with prostatic biopsies done for serum PSA elevations[11]. Results from a randomized trial of prostate cancer screening demonstrated that DRE alone resulted in detection of 56% of 473 cancers, and 17% of the 473 cancers would have been missed by PSA-based screening alone. [33]

PSA improves the positive predictive value (i.e., the proportion of men with a positive test who actually have disease) of DRE for cancer. The positive predictive value of DRE in contemporary series increases directly with the PSA level. The positive predictive value of DRE also depends on age and race [33]. In a screened population of men with suspicious DREs and PSA levels less than 4 ng/mL, Carvalhal and colleagues[34] found that black race and older age were associated with higher cancer detection rates. Schroder and associates evaluated a screened population and found that the positive predictive value of DRE ranged from 4% to 11% in men with PSA levels of 0 to 2.9 ng/mL and from 33% to 83% in men with PSA levels of 3 to 9.9 ng/mL or

more. [33]

Some investigators have suggested that the value of DRE for screening at PSA levels below 3.0 ng/mL is limited. However, because of the risk of prostate cancer among men with abnormalities on DRE and the simplicity of the examination, most urologists use PSA and DRE together for prostate cancer detection. [33]

Prostate-Specific Antigen (PSA or hK3)

The most notable marker in the evaluation of prostate cancer is hK3, also known as PSA. It was first identified and purified in the late 1970s, but widespread use in clinical urology did not occur for another decade. [35, 36] PSA is a 33-kD glycoprotein that acts as a serine protease. The ectopic expression of PSA has been reported in smaller concentrations in the tissue of malignant breast tumours, normal breast tissue, female serum, and adrenal and renal carcinomas[36]; however, for practical and clinical purposes PSA is organ specific, primarily produced by the prostatic luminal epithelial cells. Although it is organ specific, PSA is not cancer specific, as demonstrated by the substantial overlap in values between men with benign versus malignant prostatic diseases. [37]

The function of this androgen-regulated protease is to liquefy semen through its action on the gel-forming proteins semenogelin and fibronectin within the semen

following ejaculation [38]. PSA is normally found in low concentration in sera (ng/mL). Within sera, PSA circulates in both bound and unbound forms. Most PSA in sera is bound or complexed to the antiproteases ACT and macroglobulin (MG) [38]. Binding of free PSA to ACT inactivates the protease, but the complex PSA-ACT remains immunodetectable by current assays [38]. Binding of PSA to MG still allows some proteolytic activity but renders the PSA-MG complex undetectable by most current assays [38]. Free PSA without proteolytic activity is probably rendered inactive within the prostatic epithelial cell before release into the sera. This free inactive PSA does not form complexes with antiproteases, circulates unbound in sera, and is immunodetectable by current assays. The concentrations found in seminal plasma range from 0.5 to 5.0 mg/mL, whereas the normal serum concentration in men aged 50 to 80 years without prostatic disease ranges between 1.0 and 4.0 ng/mL [39].

PSA is probably cleared from the blood through the liver as the size of the complexed structure is too large for glomerular filtration. The serum half-life of PSA, calculated after removal of all prostate tissue, is 2 to 3 days. [36] Uncomplexed PSA is cleared from the serum within 2 to 3 hours and is probably excreted by the kidney because of its smaller size or cleared as a result of formation with new complexes with antiproteases.

Prostate cancer cells do not necessarily make more PSA than do normal prostate

cells, and elevated serum levels are probably a result of cancer progression and destabilization of the prostate histologic architecture[36]

PSA expression is strongly influenced by androgens. In men without BPH, the rate of change in PSA is 0.04 ng/mL per year, compared with 0.07 to 0.27 ng/mL per year in men with BPH who are between the ages of 60 and 85 years. [40]

The loss of the barrier afforded by the basal layer and basement membranes within the normal gland can occur in the setting of prostate disease (BPH, prostatitis, prostate cancer) and with prostate manipulation (prostate massage, prostate biopsy) [36]. Prostatic inflammation (acute and chronic) and urinary retention can cause PSA elevations to variable degrees. Prostatic trauma such as occurs after prostatic biopsy can result in a leak of PSA into the circulation that may require more than 4 weeks for return to baseline values. Even DRE as performed in an outpatient setting can lead to increases in serum PSA.

Prostate-directed treatment (for both BPH and cancer) can lower serum PSA by decreasing the volume of prostatic epithelium available for PSA production and by decreasing the amount of PSA produced per cell. Manipulation of the hormonal environment for treatment of cancer and BPH can lead to reductions in serum PSA. Finasteride (5 mg) and other 5α-reductase inhibitors for treatment of BPH have been

shown to lower PSA levels by an average of 50% after 6 months of treatment[41].

Clinical Use of Serum Prostate-Specific Antigen Levels

Early studies established the reference range of 0 to 4.0 ng/mL to define normal serum PSA levels. This level was obtained using the Tandem-R PSA assay (Hybritech, San Diego, CA) among a cohort of healthy men and demonstrated that healthy men 40 years old and younger and 97% of men older than 40 years have PSA levels equal to or less than 4.0 ng/mL. Although the PSA threshold of 4 ng/mL has been most commonly used, the PSA threshold that most efficiently balances the dual goal of reducing cancer mortality and reducing unnecessary testing (PSA measurements and biopsies) is not known. Many studies have made an effort to evaluate other thresholds to maximize the positive biopsy rate of PSA-based screening.

Gann and co workers [42] evaluated the ability of a single PSA measurement to predict the later development of prostate cancer among men and found that the maximum validity occurred at a PSA threshold of 3.3 ng/mL. Determination of sensitivity and specificity at given PSA thresholds does not provide information on the biologic characteristics of the cancers detected.

Using a single cut off PSA value for all men may risk exclusion of an unacceptably high number of patients with clinically significant early-stage disease;

some men with PSA values less than 4.0 ng/mL may harbour clinically significant organ-confined cancer. Catalona and associates detected prostate cancer in 22% (73 of 332) of a group of men who underwent biopsy at PSA levels of 2.6 to 4.0 ng/mL and had benign prostate examinations. [43]

Early studies recognized that the positive predictive value of PSA testing for cancer detection increased from 12% to 32% for PSA levels of 4 to 10 ng/mL and as high as 60% to 80% for levels above 10 and 20 ng/mL [43] Thus, men with PSA levels greater than 10 ng/mL and benign DRE have up to a 60% likelihood of being diagnosed with cancer and are unlikely to benefit from further improvement of PSA sensitivity and specificity. These percentages are even more pronounced for levels greater than 20 ng/mL or when DRE is suspicious for prostate cancer[7].

For men with PSA levels between 4 and 10 ng/mL, and more recently 2.5 to 10 ng/mL, the specificity of cancer detection has been more challenging. Cancers discovered within this range are often earlier in stage, and potentially more curable, yet might also represent “insignificant,” potentially non–life-threatening tumours.

Transrectal Ultrasonography Technique

Preparation, positioning, and contraindications

More than 80% of urologists administer an enema prior to transrectal ultrasonography (TRUS) and prostate biopsy, but some authors feel this is unnecessary.

More than 90% of urologists administer oral agents for prophylactic antibiotic coverage. A total of 11 different antibiotics with 20 different dosages and durations of treatment, ranging from 1-17 days, have been reported. Increasing support has been garnered for single-dose prophylaxis in patients with uncomplicated medical conditions. A fluoroquinolone antibiotic prior to the procedure and a second dose 12 hours later is the protocol most commonly recommended for antibiotic coverage. In patients with prosthetic implants or valvular heart disease, additional prophylaxis with 1 g of intramuscular ampicillin (or 1 g IV vancomycin in patients who are allergic to penicillins) and 80 mg of intramuscular gentamicin is recommended.

Positioning can be either left lateral, lithotomy, or knee-elbow.

Contraindications to biopsy include an acute painful perianal disorder and hemorrhagic diathesis. Patients should be discouraged from taking aspirin or non-steroidal anti-inflammatory drugs for 10 days prior to the procedure, but recent use should not be considered an absolute contraindication to biopsy.

Local anaesthesia and the procedure

Although the procedure was performed without any infiltrative anesthesia in the past it is a common practice to use lidocaine infiltration in the periprostatic area. In 2001, Pareek et al described a technique of periprostatic nerve blockade.[44] They injected 2.5 ml of lidocaine on each side at the prostate base at the junction of the prostate and the seminal vesicle (using a 5-in 22-gauge spinal needle through the ultrasound probe). In a randomized, double-blind, placebo-controlled study, they showed significant pain control during and after biopsy. Alavi et al compared the efficacy of intrarectal lidocaine gel with that of periprostatic nerve block and concluded that the nerve block was superior for pain control. Using this technique, saturation biopsies, with up to 20 cores, could be performed.

In 2005, Mutaguchi et al reported a comparison of 2 techniques of local anesthesia for prostate biopsy.[45] In the periprostatic block technique, 5 ml of 1% lidocaine was injected via a 7-in, 22-gauge spinal needle into the region of the prostatic vascular pedicle just lateral to the junction of seminal vesicles and the prostate. The needle is slowly withdrawn to the prostatic apex, and an additional 5 ml of lidocaine is injected at the apex. In the intraprostatic block technique, 10 ml of 1% lidocaine was injected into 2-3 sites of each prostate lobe. In this study, the intraprostatic block provided superior pain control during the prostate biopsy.

Technique of TRUS of prostate

Currently, the most widely used probe is a 7-MHz transducer within an endorectal probe, which can produce images in both the sagittal and axial planes. Scanning begins in the axial plane, and the base of the prostate and seminal vesicles are visualized first. A small amount of urine in the bladder facilitates the examination. Seminal vesicles are identified bilaterally, with the ampullae of the vas on either side of the midline. The seminal vesicles are convoluted cystic structures that are darkly anechoic. Men who have abstained from ejaculation for a long period may have dilated seminal vesicles.

Next, the base of the prostate is visualized. The central zone comprises the posterior part of the gland and is often hyperechoic. The mid gland is the widest portion of the gland. The peripheral zone forms most of the gland volume. Echoes are described as isoechoic and closely packed. The transition zone is the central part of the gland and is hypoechoic. The junction of the peripheral zone and the transition zone is distinct posteriorly and is characterized by a hyperechoic region, which results from prostatic calculi or corpora amylacea. The transition zone is often filled with cystic spaces in patients with benign prostatic hyperplasia (BPH).

Scanning at the level of the verumontanum and observing the Eiffel tower sign (anterior shadowing) help to identify the urethra and the verumontanum. The prostate distal to the verumontanum is composed mainly of the peripheral zone. The capsule is a hyperechoic structure that can be identified all around the prostate gland. Several hypoechoic rounded structures can be identified around the prostate gland. These are the

prostatic venous plexi. The position of the neurovascular bundles can often be identified by the vascular structures. Imaging in the sagittal plane allows visualization of the urethra. The median lobes of the prostate are often visualized.

Volume measurement

Volume assessment of the prostate is an important and integral part of this procedure. Several formulas have been used, the most common of which is the ellipsoid formula, which requires measurement of 3 prostate dimensions. Dimensions are first determined in the axial plane by measuring the transverse and anteroposterior dimension at the estimated point of widest transverse dimension. The longitudinal dimension is measured in the sagittal plane just off the midline because the bladder neck often obscures the cephalad extent of the gland. The ellipsoid volume formula is then applied, as follows:

Volume = height X width X length X 0.52

Biopsy

Biopsies are best performed with a spring-driven needle core biopsy device (or biopsy gun), which can be passed through the needle guide attached to the ultrasound probe. Most instrumentation provides optimal visualization of the biopsy needle path in the sagittal plane. In general, 18-gauge needles are used, and the tips of the needles are etched with small ridges or pits to render them more echogenic. Sonograms should be superimposed with a ruled puncture trajectory that corresponds to the needle guide of the probe, which allows anticipation of the needle path.

Directed biopsies are obtained from any area deemed as suggestive (i.e.,

hyperechoic) based on ultrasonographic findings or based on palpable abnormalities after digital rectal examination. Because the incidence of nonpalpable isoechoic prostate tumours is high, limiting biopsy sites to either ultrasonographically hypoechoic lesions or to areas of palpable abnormality tends to miss many malignancies.

Obtaining separate biopsy samples from each sextant of the prostate, improves the odds of sampling clinically inapparent tumours. Originally, these biopsy sites included the midlobe parasagittal plane at the apex, the mid gland, and the base, bilaterally. Many authors subsequently recommended that (1) these 6 biopsy samples be obtained from the lateral third of each lobe rather than from the mid lobe or that (2) 2 lateral biopsy samples be obtained from each lobe in addition to the original sextant samples (termed the 10-biopsy scheme). Obtaining even larger numbers of biopsy cores has been recommended by some authors to increase the diagnostic sensitivity.

Complications of prostate biopsy include hematuria, rectal bleeding, hematospermia, urosepsis, and perineal pain. Although most of these complications subside within 48-72 hours, patients should be warned that hematospermia can last for 3-4 weeks. In rare cases (<1%), patients develop bacteremia that requires hospitalization and administration of intravenous antibiotics.

Indications for Prostate Biopsy

Before TRUS improvements and serum PSA testing became widespread, clinicians relied mainly on digital rectal examination to establish a suspicion of prostate

cancer and performed digitally directed lesional biopsies. Today, PSA-based screening of asymptomatic men has resulted in the adaptation of TRUS biopsy as the standard of care for routine prostate biopsy. The presence of focal nodules on digital rectal examination still will prompt a biopsy using the TRUS technique regardless of PSA levels. TRUS-directed prostate needle biopsy remains the gold standard for diagnosis of prostate cancer.

Early prostate cancer detection has been markedly improved by PSA-based screening programs. These initiatives have been shown to significantly increase the rate of organ-confined, and potentially curable, disease[46]. Currently, most clinicians recommend biopsy once a patient's serum PSA rises above 4.0 ng/mL, although significant research efforts are ongoing to identify the optimal PSA threshold to recommend prostate biopsy in the asymptomatic patient. Evidence for lowering the PSA threshold from work by Catalona's group showed higher rates of organ-confined disease at the time of radical retropubic prostatectomy in men sampled with PSAs in the 2.6- to 4.0-ng/mL range[47]. These findings have led many urologists to now recommend prostate biopsy to men younger than 60 years of age once their PSA level rises above 2.5 ng/mL. Despite this downward shift in the PSA cut off for younger men, there remains a general trend toward allowing older men (70 years or older) to have slightly higher “normal” PSAs, in the range of 5.5 to 6.5 ng/mL, although this is not universally accepted.[48]

Adjuncts to serum PSA testing include measuring the free: total PSA, PSA velocity, PSA density (PSAD), and PSAD of the transition zone (PSAD-TZ) [49]. For patients with a serum PSA value between 4.0 and 10.0 ng/mL, using a percentage of free PSA threshold of less than 25% detected 95% of cancers while eliminating 20% unnecessary biopsies, and within this group the risk of prostate cancer increased dramatically as the percentage of free PSA level declined. [50]

Regardless of initial PSA value, a PSA velocity greater than 0.75 to 1.0 ng/mL per year is frequently associated with prostate cancer and warrants biopsy [49], whereas an elevated PSAD and PSAD-TZ have both been shown to increase the likelihood of diagnosing prostate cancer on repeat biopsy.

Contraindications to Prostate Biopsy

Significant coagulopathy, painful anorectal conditions, severe immunosuppression, and acute prostatitis are all contraindications to prostate biopsy.

Sextant Biopsy

The original sextant biopsy scheme (one core from the base, mid, and apex bilaterally) significantly improved cancer detection over digitally directed biopsy of palpable nodules and ultrasound-guided biopsy of specific hypoechoic lesions [51]. Taken in the parasagittal plane these cores sampled a portion of the PZ but also included a significant amount of tissue from the TZ, with subsequent studies of radical

prostatectomy specimens demonstrating that the vast majority of adenocarcinomas arise in the posterolateral PZ[52], thus explaining some of the false-negative results of standard sextant biopsy.

Extended Core Biopsy Techniques

Modifications to the standard sextant biopsy scheme have focused on the importance of laterally directed cores [53]. Numerous groups have published series showing improved cancer detection rates by incorporating additional laterally directed cores into the standard systematic sextant technique, ultimately taking anywhere from 8 to 13 cores [13, 54, 49]. In a prospective study of 483 patients Presti and coworkers [30]found that adding laterally directed cores from the base and mid gland bilaterally improved cancer detection from 80% with standard sextant to 96% with this 10-core scheme (only 4% of cancers were detected on the lesion directed or TZ biopsy). At present, 6 cores are considered inadequate for routine prostate biopsy for cancer detection.

Increasing Prostate Cancer Detection Rates with Extended Core Biopsy Protocols

TZ and SVs are not routinely sampled because these regions have been shown to have consistently low yields for cancer detection at initial biopsy, [55,56] but TZ and anteriorly directed biopsies may occasionally prove necessary to diagnose prostate cancer in those patients with persistently elevated PSA levels and prior negative biopsies[57]. However, there may be a role for TZ biopsies in men with gland size of more

than 50 ml, with an additional yield of 15% cancer detection in these larger prostates [58]. Seminal vesicle biopsy is not routinely performed unless there is a palpable abnormality, with some authors recommending SV biopsy when the PSA value is greater than 30 or if brachytherapy is being considered.

Study	Cores	Detection rate
Eskew et al, 1997 [59]	6	26.1%
	13	40.3%
Naughton et al, 2000 [60]	6	26%
	12	27%
Presti et al, 2000 [13]	6	33.5%
	8	39.7%
	10	40.2%
Babaian et al, 2000 [61]	6	20%
	11	30%

Repeat and Saturation Prostate Biopsy

Physicians are frequently presented with the dilemma of a patient who has had one or more negative prostate biopsies yet continues to have an elevated PSA value or abnormal digital rectal examination of concern for prostate cancer. Often these patients have undergone multiple biopsies despite the well-documented decline in cancer detection with each successive biopsy [62]. Keetch and coworkers [63] reported an initial positive biopsy rate of 34% in 1136 men from their PSA-based prostate cancer screening program. Cancer detection rates then fell to 19%, 8%, and 7% on biopsy 2, 3, and 4, respectively. These findings were confirmed by results from the European Prostate

Cancer Detection Study. In this cohort of 1051 men with PSA values between 4.0 and 10.0 ng/mL the initial cancer detection rate with sextant biopsy was 22%. Positive cores were then found in only 10%, 5%, and 4% of patients on subsequent biopsies 2, 3, and 4[62]

These diminishing returns coupled with improved cancer detection rates on initial biopsy with extended core protocols have led some researchers to examine "saturation biopsy" techniques in this difficult subset of patients. In a study of 57 men with an average of two prior negative sextant biopsies, a cancer detection rate of 30% was obtained with an average of 22.5 cores per patient [64]. Similar protocols from the Mayo Clinic[65] demonstrated improved cancer detection rates. A drawback to these techniques is that additional anesthetic requirements often require these "saturation" biopsies to be performed in a hospital setting.

Ramey et al, suggested that equally improved cancer detection rates can be achieved in this setting utilizing contrast medium–enhanced TRUS (CE-TRUS) and a targeted biopsy protocol in an outpatient setting with only 10 cores [66], thereby minimizing the morbidity and costs associated with saturation biopsies. The use of the free and total PSA may also allow classification of patients into low probability or high probability of having prostate cancer with a PSA level less than 10 ng/mL and determine the need for additional prostate biopsy after an initial negative result [50]

Advanced ultrasonographic techniques for prostate imaging

Colour and Power Doppler TRUS

Colour Doppler imaging is based on the frequency shift in the reflected sound waves from the frequency of insonation and thus depicts the velocity of blood flow in a directionally dependent manner. Colour assignment is based on the direction of blood flow related to the orientation of the transducer receiving the signal; flow toward the transducer is depicted in shades of red and flow away in shades of blue; the colour is not specific for arterial or venous flow. Power Doppler imaging (also known as enhanced colour Doppler, colour amplitude imaging [CAI], or colour angiography) utilizes amplitude shift to detect flow in a velocity and directionally independent manner [67]. The advantages of power Doppler imaging are its ability to detect slower flow and to have less reliance on the Doppler angle, making it more suitable for detection of prostate cancer neovascularity. Although power Doppler imaging offers improved sensitivity to small amounts of flow, neither modality has yet proved itself superior to the other for cancer detection.

In a study by Maruzzi et al, [68] 222 biopsies performed on 71 patients between 1997 and 1999 were considered, which led to a diagnosis of neoplasm in 36 patients. Of the 84 biopsies that revealed prostate adenocarcinoma, 74 (64.3%) were correlated to hypoechoic lesions with abnormal flow signals while 41 (35.6%) showed a benign pathology (prostatitis or benign prostatic hyperplasia) ($p < 0.0011$). In five patients

(13%) who did not present any evident lesions at a first transrectal ultrasound, the diagnosis of neoplasm was made only through biopsies targeted on areas with abnormal flow. Therefore, they concluded that the colour Doppler exam can be used during prostate ultrasonography either to consolidate the diagnosis or to give a useful target in case of isoechoic lesions.

Takahashi and colleagues[69] studied a total of 108 men (mean age 67.7 years, range 50 to 86) with serum PSA levels of greater than 4.0 ng/mL using digital rectal examination (DRE), grey-scale transrectal ultrasonography (TRUS), and PDU. and systematic six-core transperineal biopsy and additional biopsies for positive sites on DRE, grey-scale TRUS, and PDU. A hypervascular site and prostate cancer on PDU was identified in 43 (40%) and 40 (37%) cases, respectively. The sensitivity of PDU for cancer detection was 90%, specificity 90%, positive predictive value 84%, negative predictive value 94% and accuracy 90%. High test performance was also observed in 53 cases with serum PSA levels of 4.1 to 10 ng/mL (sensitivity 77%, specificity 88%, positive predictive value 67%, negative predictive value 92%, and accuracy 85%). These values were superior or comparable to those of DRE and grey-scale TRUS. Inflammatory reactions and prostatic calculi were probable major causes of false-positive and false-negative results on PDU, respectively.

Okihara et al[70] studied 275 men. Cancer was identified in 27% of men in Japanese and in 60% of American men. The sensitivity and specificity of PDI in Americans were significantly inferior to those in Japanese. The negative predictive value (NPV) of PDI

was significantly higher for Japanese.

In a significant study by Wilson et al, [71] 96 patients with LUTS and PSA > 4 ng/ml were evaluated using PDUS before biopsy. There was a significant correlation between the grading system used for power Doppler and the microvessel density (MVD; PZ0 28.61 +/- 8.97, PZ1 36.00 +/- 12.11 & PZ2 64.008 +/- 15.86; $p < 0.001$). There was also a significant difference in MVD between benign, malignant and tissue cores with atypia and prostatic intra-epithelial neoplasia (PIN; $p < 0.001$ and $p < 0.018$ respectively). There was a significant correlation between malignant tissue having a higher Gleason score and increased MVD ($p < 0.001$) Furthermore, cancer biopsies having a high flow PZ2 are nearly twice as likely (63.2%) to have a Gleason score of 7 or more when compared those having a Gleason score of less than 7 (36.8%). They concluded that it can be useful in the detection of prostate cancer.

In a study by Inahara et al, [72] 101 men with abnormal DRE or PSA were assessed with TRUS with PDI. Of the 101 patients, 48 (47.5%), 42 (41.5%) and 42 (41.5%) were suspicious of having prostate cancer by DRE, TRUS and PDI, respectively. If prostate needle biopsy was avoided when PDI was negative, then PDI eliminated the need for biopsy in 59 of the 101 patients (rate of biopsy procedures saved: 58.4%) and missed only 8 (13.6%) prostate cancers. Moreover, in 63 patients with intermediate PSA (3-10 ng/ml), the rate of biopsy procedures saved by DRE, TRUS, and PDI was 60.3%, 65.1%, and 68.3%, respectively, and the rate of cancers missed was 26.3%, 19.5%, and 14.0%, respectively. 34.1% of prostate cancer sites were isoechoic and hypervascular.

On a site by site basis, PDI had better sensitivity, specificity, positive predictive value and negative predictive value than TRUS. In patients without abnormal DRE findings, on a site by site basis, the sensitivities of TRUS and PDI were 22.9% and 34.4%, respectively.

In a study by Remzi et al, [73]136 men with PSA between 2.5 and 10 ng/ml (mean age 64 +/- 9 years, range 45-82) and a normal DRE were included. 101 underwent a first biopsy whereas 35 had repeat biopsy. Overall prostate cancer detection rate was 34.7% and 25.7% and abnormal accumulation on PD-TRUS was identified in 42.3% and 48.6% on first and repeat biopsy, respectively. PD-TRUS directed biopsies were positive in 5.7% and 11.1% on first and repeat biopsy whereas prostate cancer detection using the routine prostate biopsy regime was 94.3% and 88.9% on first and repeat biopsy. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PD-TRUS signal alone for prostate cancer detection on first biopsy was 82.8%, 78.8%, 87.9% and 89.7%, respectively, and 88.8%, 68.0%, 47.0% and 94.4% on repeat biopsy, respectively. Negative PD-TRUS signal is able to exclude most of the patients without prostate cancer in the PSA range of 2.5-10 ng/ml. As an additional tool at TRUS biopsy PD-TRUS has a high negative predictive value and may help to reduce the number of unnecessary biopsies.

In a study by Satoru [74]et al, 108 men with serum PSA levels of greater than 4.0 ng/mL were assessed using DRE, TRUS, and PDU. A hypervascular site and prostate cancer on PDU was identified in 43 (40%) and 40 (37%) cases, respectively. PDU-

directed and systematic six-core biopsies could independently detect 36 and 30 cancer cases, respectively. The sensitivity of PDU for cancer detection was 90%, specificity 90%, positive predictive value 84%, negative predictive value 94% and accuracy 90%. High test performance was also observed in 53 cases with serum PSA levels of 4.1 to 10 ng/mL (sensitivity 77%, specificity 88%, positive predictive value 67%, negative predictive value 92%, and accuracy 85%). These values were superior or comparable to those of DRE and gray-scale TRUS. PDU can identify appropriate sites for biopsy and improve the cancer detection rate. Combined use of sextant biopsy and PDUS should be preferable.

Mohammd et al[75] in their study concluded that, Colour-coded Doppler flow within the tumor and overlying capsule appears to correlate with both tumor grade and stage, respectively. Detection and grading of colour-coded flow within biopsy-proven cancers may identify patients with a high likelihood of biochemical relapse. Tsuneyuki Nakanouchi et al[76]from their study on 22 patients prior to RP concluded that, semi quantitative assessment of Doppler flow signals using PDI appears to be of clinical value as an indicator of MVD.

Arger etal[77] studied 90 patients and found that 71% of the 31 focal hypoechoic lesions were hypervascular. Only 23% were carcinoma. Sauvain[78] et al studied 323 patients with suspected cancer. The sensitivity of PDS for prostatic cancer was 92.4%

and its specificity was 72% (versus 87.9% and 57.6% for sonography alone respectively). The NPV of PDS was 80.6% ($p<0.0001$). Targeting area presenting abnormal blood flow in any part of the prostate was useful to detect isoechoic or lesions in patients with first negative biopsy results.

Halpern et al[79], in their study on 62 patients with cancer in 18 (29%) patients found that The positive biopsy rate for targeted biopsy (24 [13%] of 185 cores) was slightly higher than that for sextant biopsy (36 [9.7%] of 372 cores; P =.1). The odds ratio for cancer detection with targeted versus sextant cores was 1.8 (95% CI: 0.9, 3.7). Receiver operating characteristic analysis demonstrated that overall identification of positive sextant biopsy sites was close to random chance for grey-scale (area under the curve, 0.53), colour Doppler (area under the curve, 0.50), and power Doppler (area under the curve, 0.47) imaging.

Okihara et al[80], in their study on a total of 170 cases, the positive biopsy rate was 59% (40/68) in cases with HVL, compared to 1% (1/102) in cases with no HVL ($p < 0.0001$). In 107 patients with serum PSA 4.1 to 10.0 ng/ml, biopsy was positive in 13 cases (12%). The positive biopsy rate was 38% (12/32) in cases with HVL, compared to 1% (1/75) in cases with no HVL ($p < 0.0001$). These results imply that HVL represents the neovascularity or increased perfusion of blood in the cancer lesion.

Sakarya et al[81], in their study on 36 patients calculated that the sensitivity of PDU

was 90%, the specificity 75% and the positive predictive value 82%. Okihara et al [82] in their study on 107 patients found that PDI had a high sensitivity of 98% (40/41) and a negative predictive value of 99% (101/102). PDI could save a significant number of patients from undergoing unnecessary biopsies, compared with DRE and TRUS ($P < 0.001$). 28 patients were studied by Franco[83] and colleagues, and the sensitivity of PDUS was 74%, the specificity 96% and the positive predictive value 74%.

Whereas Doppler modes showed an improved diagnosis versus grey-scale TRUS, 45% of cancers still went unidentified by any sonographic modality. Others have shown increased cancer detection rates using Doppler-targeted biopsy strategies [81], but none is sufficiently accurate to replace systematic biopsy [79]. Enhancements in the technical aspects of colour Doppler TRUS, including the use of contrast agents (see later), may provide the necessary improvements to specifically identify cancer sites in the future.

Multiple studies have shown that angioneogenesis and the resultant increase in microvessel density that occurs within foci of prostatic adenocarcinoma correlates with the presence of metastases[84], stage of disease [84,85], and disease-specific survival. Interest in using colour and power Doppler TRUS to aid in prostate cancer detection stems from studies of radical prostatectomy specimens demonstrating that foci of adenocarcinoma possess an increased density of microvessels compared with surrounding normal parenchyma. [86] Patients with detectable colour Doppler flow within their dominant tumor at the time of TRUS-guided biopsy are at a 10-fold increased risk for PSA recurrence

after radical retropubic prostatectomy [76] The presence of increased flow was also associated with higher Gleason grade, increased incidence of SV invasion, and a lower biochemical disease-free (bNED) survival rate versus subjects without increased flow on preoperative TRUS (50% vs. 96% bNED at 31 months).

Current Doppler modalities are not able to identify the microvessels of prostate cancer, which are typically 10 to 15 μm in diameter. The flow signals associated with malignant foci detected by unenhanced colour and power Doppler imaging are due to detection of larger feeding vessels. [88] Intravenous micro bubble ultrasound contrast agents, similar to those currently approved and used in echocardiography, have been infused systemically during grey-scale and TRUS Doppler imaging to amplify flow signals within the microvasculature of prostate tumours, allowing selective visualization of malignant foci in clinical trials [79, 88]. These intravenous "bubble" contrast agents are constructed with air or higher-molecular-weight gas agents encapsulated (albumin or polymer hard shell, lipid or surfactant coated) for longevity and are generally 1 to 10 μm.

Using CE-TRUS for prospective prostate cancer detection, Halpern and associates[79] demonstrated an increase in sensitivity from 38% to 65% versus baseline unenhanced imaging, without significantly altering specificity. Subsequent studies by our group and others have improved sonographic detection of malignant foci utilizing

CE-TRUS and targeted biopsy of enhancing lesions[89, 90]. Imaging using micro bubble contrast agents combined with three dimensional image reconstruction of enhanced power Doppler images also demonstrated increased diagnostic accuracy. Future developments in these and other imaging modalities that can selectively visualize prostate cancers based on the presence of angioneogenesis may ultimately allow more accurate localization of the sites of cancer.

Other Investigational Techniques

Artificial neural networks are another potential way to enhance TRUS images and identify malignant foci. Investigational automated image analysis, including pattern recognition and artificial neural networks applied to TRUS images, may successfully identify lesions that cannot be seen by the human eye. [91]

A new sonographic technique known as elastography may prove to be superior to colour Doppler imaging in the identification of malignant areas in the prostate. [92] This technique employs real-time sonographic imaging of the prostate at baseline and under varying degrees of compression. Through computerized calculations, differences in displacement between ultrasonic images from baseline and during compression may be visualized and regions with decreased tissue elasticity may be tagged as suggestive of malignancy. In a preliminary study of 404 cases with 151 cases positive for prostate cancer, the malignancy was found in 127 patients (84.1%) with real-time elastography

directing the biopsy. [93]

Endorectal magnetic resonance imaging (MRI) and MR spectroscopy as combined modalities might be able to guide and therefore limit the number of iterative biopsies and cores for patients [94]. Utilization of MRI will require modifications in instrumentation and the technique of biopsy [95]. These MRI-directed biopsy techniques require expensive equipment that is not widely available for biopsy procedures.

MATERIALS AND METHODS

A prospective study was conducted in the time period between July 2006 and May 2009. All the patients more than 50 years who presented to the Urology OPD with LUTS with abnormal digital rectal examination and/or PSA>=4 ng/ml were evaluated for inclusion in the study.

Exclusion criteria

1. No consent for study
2. Persistent urinary tract infection
3. Untreated coagulopathy

After obtaining informed consent all the patients were enrolled into the study. Routine clinical evaluation was done as per the proforma and the findings were recorded.

All the patients were evaluated by TRUS. On the day prior to the procedure, ciprofloxacin 500mg bd and metronidazole 400 mg tds was prescribed, which was continued for 2 days post procedure. PC enema was given on the day of the procedure. Intravenous pethidine was given as analgesic if the patient did not tolerate pain.

Patients were examined using the SSD2000 System (Aloka, Japan); PDUS was carried out with a Power Flow Unit and 7.5 MHz broadband endoluminal probe. The patients were examined in the left lateral decubitus position. All patients underwent greyscale TRUS of the entire prostate gland in the sagittal plane, from the right to left lateral aspects of the gland and in the axial plane from the seminal vesicles to the apex.

The size and weight of the gland were calculated from the anteroposterior, transverse and cranio caudal measurements (0.52 × D1 × D2 × D3).

PDI was performed using the same ultrasound system as for conventional TRUS. The power Doppler gain was set to a point below the range at which blood flow in the neurovascular bundles was identified with no background artefact. Scanning to detect flow was continued for 10 min in each patient. The vascularization of a hypoechoic lesion in the PZ was evaluated by comparison with that of the area surrounding it. When a hypoechoic lesion contained more vessels than other PZ areas, it was defined as a hypervascular area. Equivocal and isoechoic lesions were defined as hypervascular area when these lesions were seen as abnormal vascular areas.

All patients underwent systematic core biopsies initially at the hypervascular areas and hypoechoic areas if seen and then standard 10 core biopsy was taken from the prostate. 18 G (Bard Urological, Covington, GA) automatic core biopsy needles were used. Biopsy samples from each site were placed in separate containers of formalin and labelled as to the site of origin. The biopsy results were analysed statistically to evaluate the differential efficacy of the hypoechoic nodule and hypervascular areas.

RESULTS

A total of 129 patients were included in the study period.

75 patients (58%) had cancer detected in the biopsy

Table-1: Age group of patients

Age Group	Number
<55	1(0.7%)
56-60	33(25.5%)
61-65	39(30.2%)
66-70	33(25.5%)
71-75	12(9.3%)
76-80	11(8.8%)
Grand Total	129(100%)

The mean age group of the patients was 65.63 years in the age range between 55 and 80 years. The most common age group involved was between 56 and 70 years involving 80% of the patients.

49 of the 129 (37%) patients had a normal DRE.

PSA value

The PSA value of the patients ranged from 3 ng / ml to 632 ng / ml with a mean value of 41.4 ng / ml.

Table-2: PSA group of patients

PSA Group(ng/ml)	Number
<4	1(0.7%)
4--10	14(10.8%)
11--20	37(28.6%)
21-50	58(44.9%)

>50	19(15%)
Grand Total	129(100%)

Prostate volume

Table-3: Prostate volume of patients

Prostate volume	Number
<25 g	55(42.6%)
26-50 g	62(48%)
>50 g	12(9.4%)
Grand Total	129(100%)

The mean prostate volume was 32.7g in the range between 12 and 155g.

Relation of cancer with various parameters

Age group

The proportion of patients who are negative for cancer are proportionately more in the age group 56-60 years. The highest incidence of cancer was in the age group 66-70 years. All the patients in the age group above 70 years had cancer. However, the difference in age distribution was not statistically significant.

Table-4: Relation of cancer with age group

Age Gp (Yrs)	Ca present	No Ca	Total
<55	1	0	1
56-60	15	18	33
61-65	19	20	39
66-70	19	14	33
71-75	12	0	12
76-80	9	2	11

Grand Total	75	54	129

p-0.129

PSA level

Table-5: Relation of cancer with PSA group

PSA Gp(ng/mi)	Ca present	No Ca	Total
<4	1	0	1
4--10	2	12	14
11--20	21	16	37
21-50	38	20	58
>50	13	6	19
Grand Total	75	54	129

p-0.02

75% of patients with PSA between 4 and 10 ng/ml were negative for malignancy. Even with a PSA of > 50 ng/ml had negative result for malignancy. Most of the patients with cancer were in the PSA range of 21-50ng/ml.

Prostate volume and Cancer

Patients with cancer are equally distributed among all the prostate sizes.

Table-6: Relation of prostate volume with cancer

Prostate vol.	Ca present	No Ca	Total
<25	29	26	55
26-50	38	24	62
>50	8	4	12
Grand Total	75	54	129

p-0.66

DRE and tumour

Table-7: Relation of DRE with cancer

DRE	Ca present	No Ca	Total
+ ve	56	24	80
- ve	19	30	49
Grand Total	75	54	129

p-0.004

70% of patients with positive DRE had positive biopsy.

Correlation between Hypoechoic area and carcinoma

Table-8: Relation of hypoechoic area with cancer

Hypo. area	Ca present	No Ca	Total
Yes	47	18	65
No*	28	36	64
Grand Total	75	54	129

***- Absent hypoechoic area / negative biopsy

The sensitivity of hypoechoic nodule in the detection of prostate cancer is 62.7%, Specificity is 66.7%, Positive Predictive value 72.3% and Negative predictive value is 56%.

Correlation between hypervascular area and carcinoma

Table-9: Relation of hypervascular area with cancer

Hypervascularity	Ca present	No Ca	Total
Yes	66	12	78
No*	9	42	51
Grand Total	75	54	129

***- Absent hypervascular area / negative biopsy

The sensitivity, specificity, PPV, NPV of hypervascular area in the detection of ca prostate are 88.5%, 79.8%, 84.6%, 82.3% respectively.

Correlation between hypervascularity in hypoechoic area and cancer

Table-10: Relation of hypervascularity in hypoechoic area with cancer

Hypervascularity in hypoechoic lesion	Ca present	No Ca	Total
Yes	34	1	35
No	41	53	94
Grand Total	75	54	129

The sensitivity, specificity, PPV, NPV of hypervascularity in the hypoechoic nodule in the detection of ca prostate are 45.3%, 98%, 97%, 56.3% respectively

Statistical comparison of parameters

Table-11: Comparison of parameters

	Hypervascular area	Hypoechoic area	Hypervascularity in hypoechoic area
Sensitivity	88.5%	62.7%*	45.7%*
Specificity	79.8%	66.7% β	98%*
PPV	84.6%	72.3% β	97%¶
NPV	82.3%	56%.*	56.3%*

¶-p-Not significant, *-p<0.01, β-p<0.05 (compared with PDI)

Complications

A total of 16 patients had complications. Febrile UTI was the most common complication involving 8 patients. All were managed conservatively.

Table-12: Complications

Complication	Number
UTI	8
Retention	7
Bleeding	4

DISCUSSION

Prostate cancer is the most common non cutaneous cancer involving men. Nowadays, most of the prostate cancer is diagnosed incidentally, at least in the western countries. In our country most of the patients present with symptoms such as LUTS or other metastatic symptoms.

As the diagnostic modalities such as serum PSA and DRE have significant false positive and false negative rates, histological diagnosis by TRUS guided biopsy is considered the gold standard to diagnose prostate cancer. Though it is considered the primary investigation, it has only 85% sensitivity and 80% specificity, even with extended core biopsy.

To increase the yield various associated modalities are used, such as the power Doppler imaging. In our study we evaluated the efficiency of power Doppler imaging in the detection of prostate cancer.

The mean age of the patients was 65.6 years ranging from 55 to 80 years, majority were in the age group between 56 and 70 years, around 80%. The age group of our population was comparable to those in the literature, involving prostate cancer. On stratifying the patients according to the age group, patients in the age group between 56 and 70 years had proportionately higher incidence of negative biopsies and the age group of 66 to 70 years had higher incidence of positive biopsies. This shows the increasing incidence of prostate cancer with age.

Only 10% of the patients had prostate size of more than 50ml. this shows that size

of the prostate does not signify the presence or absence of malignancy. The mean prostate size was 32.7 grams ranging from 12 to 155 ml. Prostate size did not correlate with the presence of ca prostate, correlation coefficient -0.06..

Serum PSA is the other important investigation done to diagnose prostate cancer. PSA ranged from 3 ng/ml to 756ng/ml. The mean PSA was 41.4 ng/ml. The mean serum PSA in cancer positive patients was 44.26ng/ml and 18.2 ng/ml in cancer negative patients. Though PSA more than 4 ng/ml is considered to be suggestive of ca prostate, the higher incidence of infections (prostatitis) in Indian patients may cause elevation of serum PSA. So a high PSA may not be suggestive of cancer until it is proved by biopsy. More than 70% of patients with PSA >20 ng/ml had carcinoma prostate.

56 out of 75 patients with carcinoma had positive DRE. This gives a sensitivity of 76%. This is considered high comparing the literature values of between 40 to 70%. This might be due to the predominant presentation of patients with higher tumour stages in the Indian scenario.

Hypoechoic area directed biopsy was the modality of diagnosis practiced in the late 1980s[51-52]. The hypoechoic nodule directed biopsies were found to have a sensitivity of around 70% and specificity on the range of 60%. In our study, the sensitivity was 62.7%, Specificity was 66.7%, Positive Predictive value 72.3% and Negative predictive value was 56%.. this shows the poor efficacy of hypoechoic nodule directed biopsy in the detection of prostate cancer.

Tumours are found to be hypervascular due to the neovascularity. Power Doppler

imaging, which deciphers the tissue vascularity, may be used in the evaluation of vascularity of lesions. Biopsies directed towards the hypervascular areas were found to have a higher sensitivity of around 90% and specificity of 85% in various studies[69-81]. In our study, the sensitivity was 88.5% for detection of cancer in comparison with 10 core biopsy. This shows that hypervascular area directed biopsy definitely scores over hypoechoic area directed biopsy in the detection of prostate cancer.

Overall 58% patients were detected to have cancer. It is higher when compared to the literature, which varies from 36% to 55%. The higher percentage in our study could be due to the large number of patients with both elevated PSA and positive DRE. The Indian patients moreover present late compared with the west. The overall sensitivity of power Doppler in the detection of prostate cancer in our study was 88.5 % similar to the previous studies. The specificity of 79.8% was comparable with the world literature. The positive predictive value of 84.6% was similar to other studies. The negative predictive value of 82.3% was comparably less than the world literature which varies from 78 to 94%.

Table-13: Comparison of studies with power doppler

Ca (%)	No.(Pts)	Sen	Spe	PPV	NPV	Study
36	136	82.8%,	78.8%,	87.9%	89.7%,	Remzi[73]
40	108	90%,	90%	84%,	94%	Satoru[74]
55	323	92.4%	72%	83%	80.6%	Sauvain[78]
36	36	90%,	75%	82%	88%	Sakarya[80]
42	28	74%,	96%	74%	78%	Franco[83]
40	108	90%	90%	84%	94%	Takahashi[69]
58	129	88.5%	79.8%	84.6%	82.3%	*

* - present study

One important point to note in our study is that in 3 patients with carcinoma, the tumour was picked up by hypervascular area directed biopsy, but it was not diagnosed by 10 core biopsy. In all these patients the prostate volume was more than 50ml. Though the values are not statistically significant, we can advise hypervascular area directed biopsy combined with standard 10 core biopsy in patients with large prostates. This finding correlates with the study by Saturo et al where 3 patients with a negative sextant biopsy had a positive targeted biopsy.[75].

The presence of hypervascularity in hypoechoic nodules is associated with a positive predictive value of 98%. So if a patient has a hypoechoic nodule showing hypervascularity, this is most likely to have a focus of tumour.

On evaluating the statistical parameters using the test of proportions, the difference in sensitivity and NPV between PDI and grey scale imaging was statistically significant with p value of <0.01. Difference in specificity and PPV had a p value of < 0.05.

The complication rate in our study was 10%. This is equal to those reported in literature. The most common complication was UTI, which was managed conservatively with antibiotics. These infections do occur even after antibiotic prophylaxis, so patients need to be counselled prior to procedure. 4 patients had minimal hematuria which was managed conservatively.

To conclude, transrectal ultrasound with power Doppler imaging guided biopsy is

more sensitive and specific compared to grey scale imaging. Extended core biopsy protocol though, still remains the gold standard. We would like to recommend hypervascular area directed biopsies combined with standard extended core biopsies in large prostates to increase the yield.

CONCLUSION

Power Doppler imaging guided hypervascular area directed biopsy is efficient in the detection of prostate cancer in comparison with hypoechoic nodule directed biopsy.

SUGGESTIONS:

Power Doppler guided targeted biopsy of hypervascular area, may be combined with extended core biopsy to increase the yield of core biopsy.

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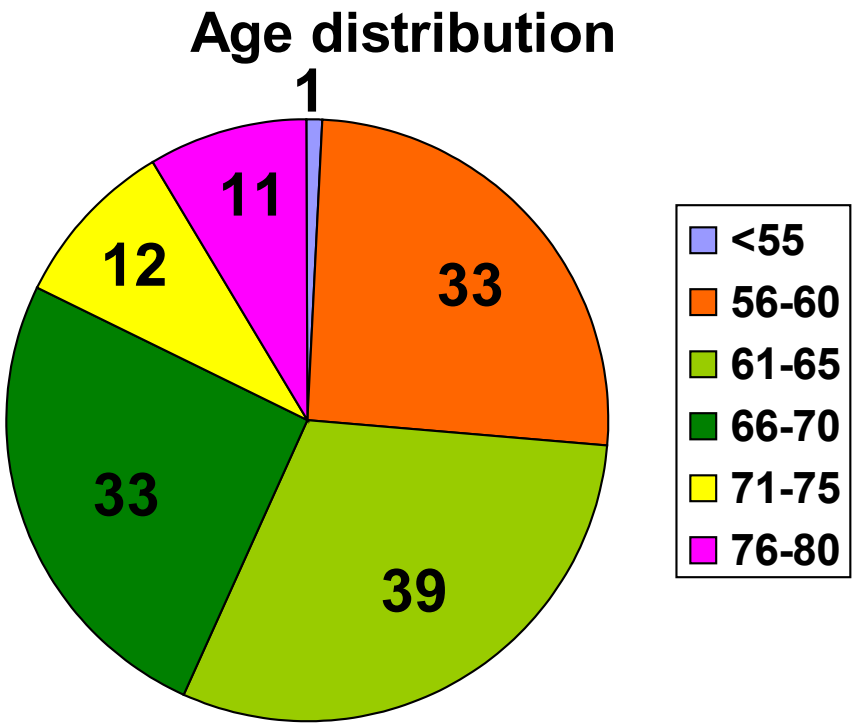


Figure-1:

Age distribution of patients

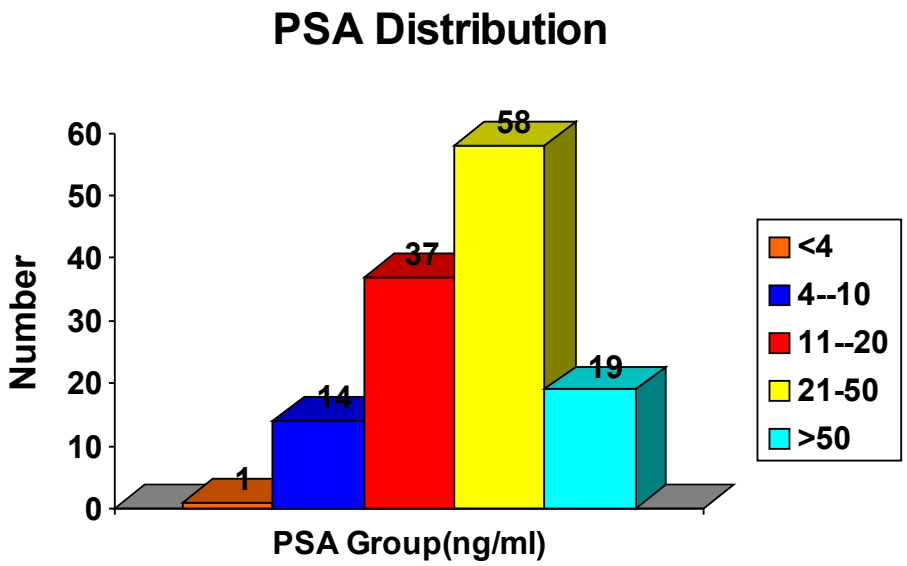
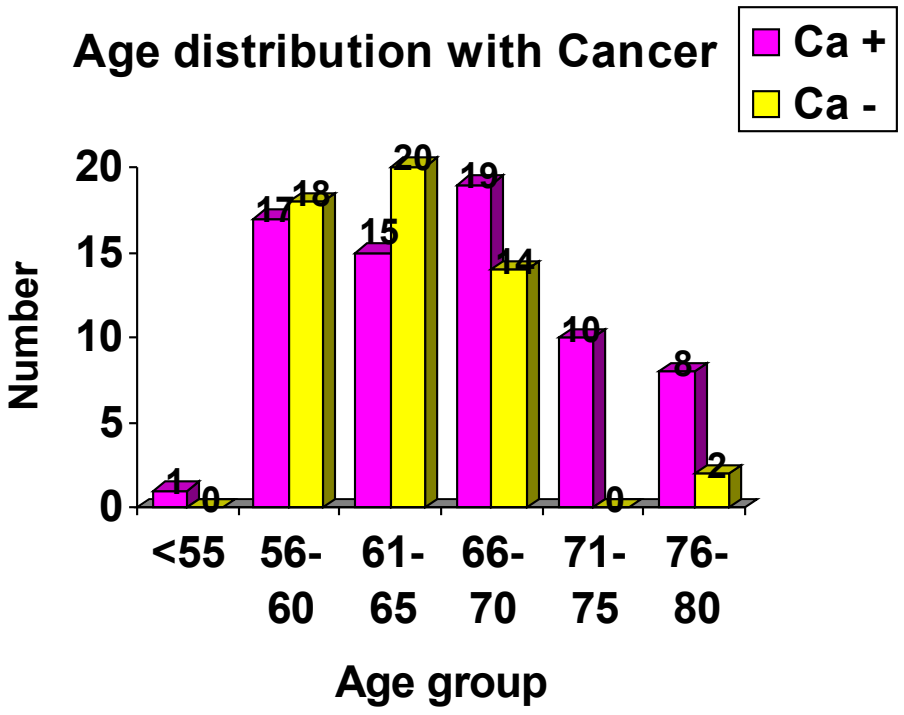


Figure-2: PSA distribution of patients

Figure-3: Age distribution in relation to cancer


Age distribution with Cancer
Ca +
Ca -
Number
20
15
10
5
0
1
0
17
18
15
20
19
14
10
0
8
2
<55
56-60
61-65
66-70
71-75
76-80
Age group

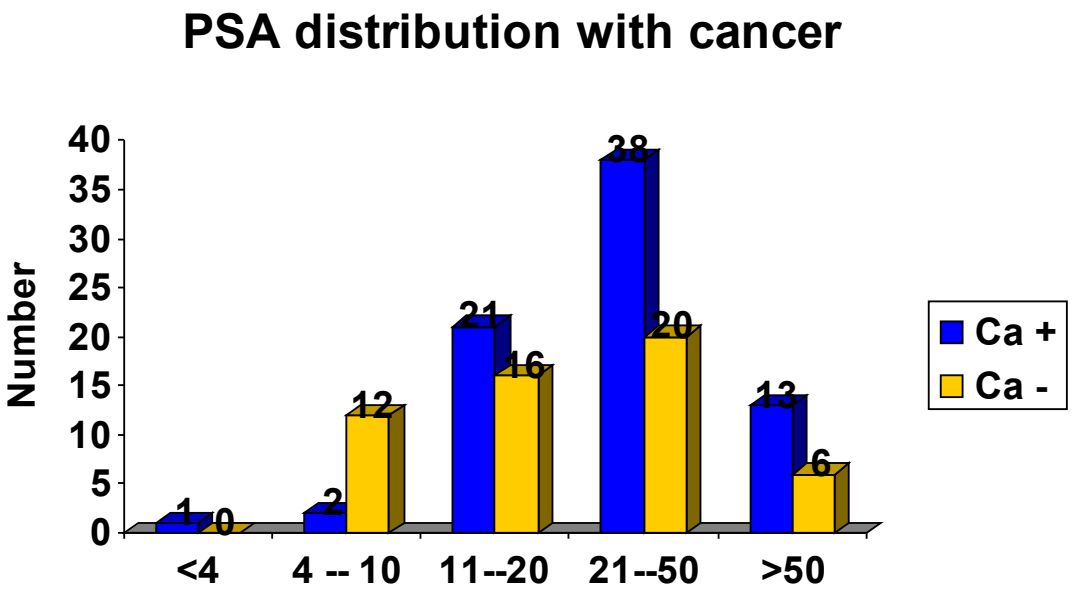


Figure-4:

PSA distribution in relation to cancer

Figure-5: Statistical analysis

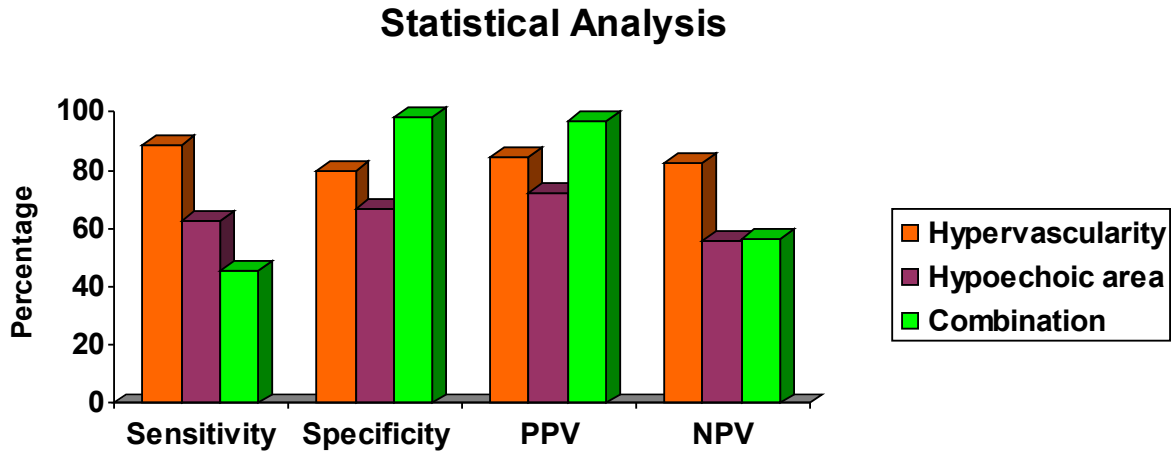


Figure-6: SSD2000 System (Aloka, Japan)

Figure-7: 7.5 MHz broadband endoluminal probe with biopsy gun

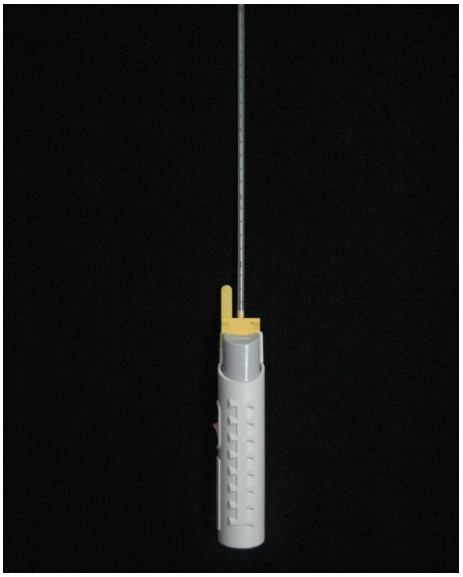


Figure-8: Bard max core biopsy needle, 18 g x 25 cm length

Figure-9: Penetration depth 22mm with sample notch 18mm

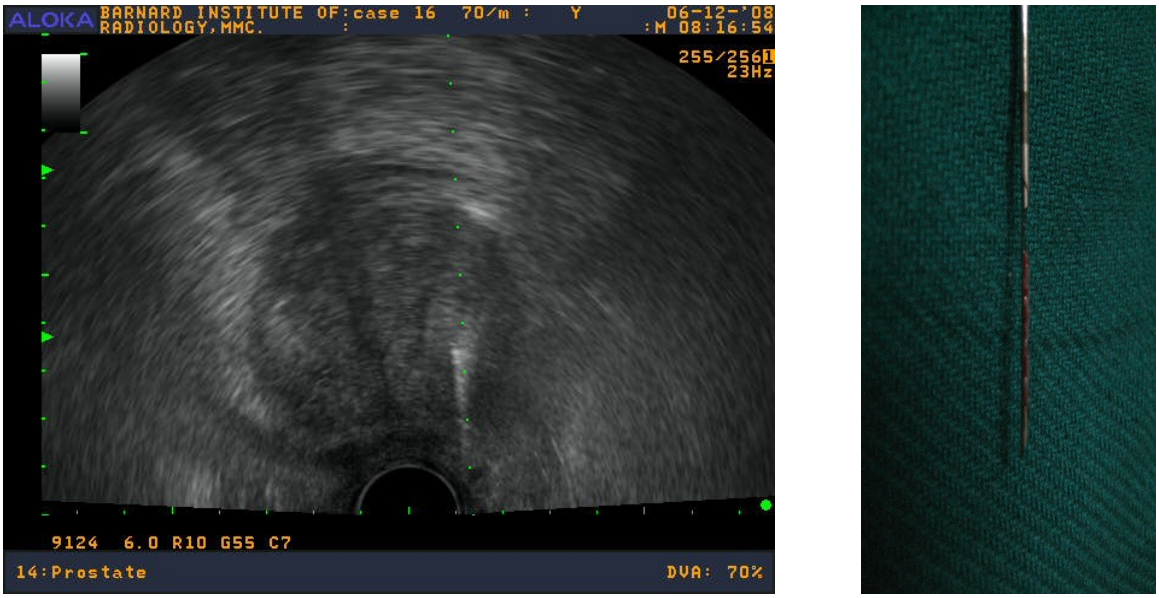


Figure-10: Biopsy core being taken

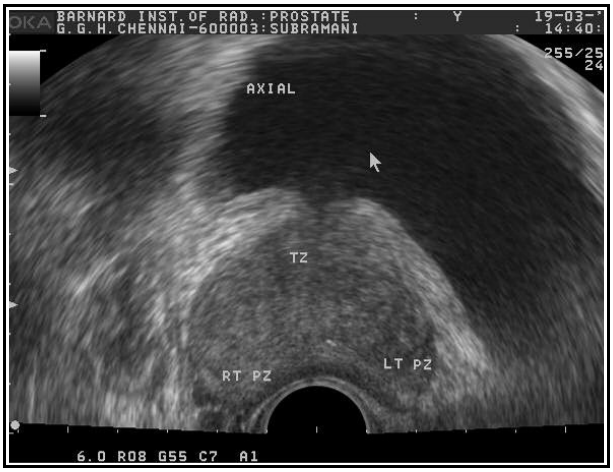


Figure-11: Normal prostate gland

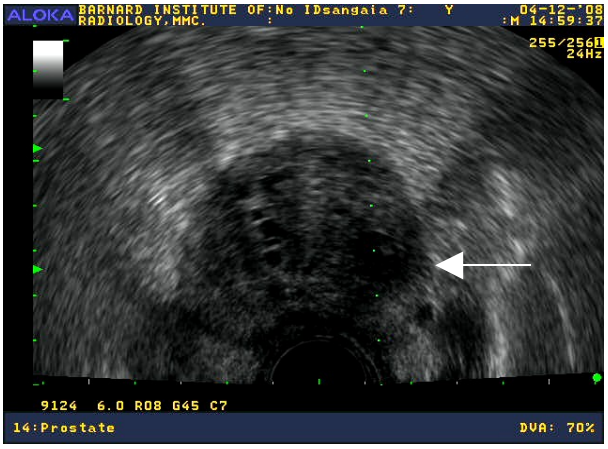


Figure-12: Hypoechoic area

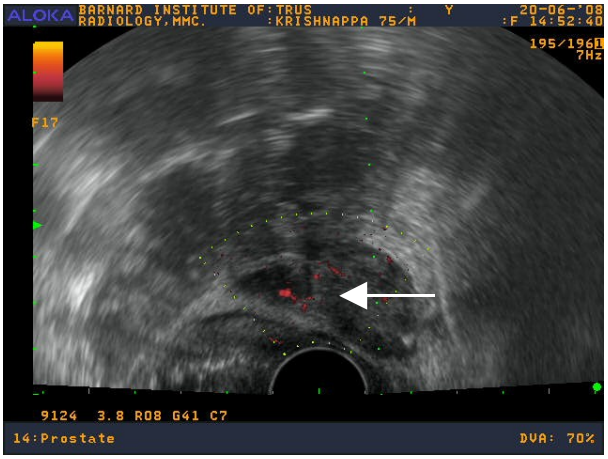


Figure-13: Hypervascular area

MASTER CHART

No	Age	LUTS (months)	DRE	PSA	Pr Vol	Hypo	PDI	Combined	10 core
1	75	6	Yes	8	22	Yes	Yes	Yes	Yes
2	60	4	No	34	14	Yes	No	No	No
3	70	6	Yes	54	34	Yes	Yes	No	Yes
4	60	8	Yes	22	35	Yes	Yes	No	Yes
5	75	6	Yes	765	45	Yes	Yes	Yes	Yes
6	78	8	Yes	3	76	No	No	No	Yes
7	78	5	No	23	80	No	No	No	No
8	65	6	Yes	22	12	Yes	Yes	Yes	Yes
9	53	7	No	11	23	Yes	Yes	No	Yes
10	60	6	No	4	43	No	No	No	No
11	80	5	Yes	34	154	Yes	Yes	No	Yes
12	57	4	Yes	34	34	Yes	Yes	Yes	Yes
13	75	12	Yes	13	25	No	Yes	No	Yes
14	61	8	Yes	15	24	Yes	No	No	Yes
15	64	11	Yes	25	32	No	Yes	No	Yes
16	60	5	No	43	13	No	No	No	No
17	58	9	No	66	23	No	Yes	No	Yes
18	69	7	No	23	21	Yes	Yes	Yes	Yes
19	75	12	Yes	7	21	Yes	Yes	Yes	Yes
20	60	7	No	10	32	No	No	No	No
21	66	6	No	18	12	Yes	Yes	Yes	Yes
22	75	18	Yes	35	13	Yes	Yes	Yes	Yes
23	58	8	Yes	18	43	Yes	Yes	Yes	Yes
24	68	9	Yes	38	32	Yes	Yes	Yes	Yes
25	77	12	Yes	15	23	Yes	Yes	Yes	Yes
26	60	5	No	15	21	Yes	No	No	No
27	72	8	Yes	16	32	Yes	Yes	No	Yes
28	57	6	No	6	12	No	No	No	No
29	78	18	Yes	26	24	No	Yes	No	Yes
30	65	10	No	22	22	Yes	Yes	Yes	Yes
31	65	4	Yes	23	23	No	No	No	Yes
32	60	6	Yes	97	25	Yes	Yes	Yes	Yes
33	74	11	No	104	26	Yes	Yes	Yes	Yes
34	69	1	Yes	45	27	No	Yes	No	Yes
35	60	6	No	64	24	Yes	Yes	No	Yes
36	65	9	No	24	17	No	No	No	No
37	65	10	No	35	18	No	Yes	No	Yes
38	78	1	Yes	64	19	Yes	Yes	Yes	Yes
39	70	18	No	28	14	No	Yes	No	Yes
40	64	8	Yes	34	23	No	Yes	No	Yes
41	63	5	Yes	29	26	Yes	Yes	Yes	Yes
42	66	7	Yes	17	29	Yes	Yes	Yes	Yes
43	60	6	Yes	22	155	Yes	Yes	Yes	Yes
44	71	12	No	13	34	No	No	No	Yes
45	59	3	No	14	32	No	No	No	No
46	68	18	No	24	20	No	Yes	Yes	Yes
47	63	6	Yes	45	27	Yes	Yes	Yes	Yes

48	70	10	Yes	47	34	No	Yes	No	Yes
49	58	4	Yes	68	56	Yes	Yes	Yes	Yes
50	66	5	Yes	45	54	No	Yes	No	Yes
51	57	6	Yes	62	34	No	No	No	No
52	68	8	Yes	44	23	No	Yes	No	Yes
53	67	18	No	35	38	Yes	Yes	No	Yes
54	78	9	No	25	28	No	No	No	Yes
55	69	8	No	34	26	Yes	Yes	Yes	Yes
56	65	6	Yes	26	19	No	Yes	No	Yes
57	58	4	Yes	22	20	No	Yes	No	Yes
58	68	9	No	13	53	No	No	No	No
59	64	11	Yes	24	44	Yes	Yes	Yes	Yes
60	63	8	Yes	24	45	Yes	Yes	Yes	Yes
61	60	6	Yes	12	24	No	Yes	No	Yes
62	58	5	Yes	14	25	Yes	No	No	Yes
63	70	18	Yes	15	27	No	Yes	No	Yes
64	68	4	No	34	26	Yes	No	No	No
65	59	6	Yes	23	28	Yes	Yes	Yes	Yes
66	67	10	Yes	22	29	No	Yes	No	Yes
67	65	9	Yes	12	44	No	No	No	No
68	65	7	Yes	13	34	Yes	Yes	No	Yes
69	62	8	Yes	23	18	No	Yes	No	Yes
70	65	1	Yes	13	18	Yes	No	No	No
71	60	3	Yes	15	27	No	Yes	No	Yes
72	60	8	Yes	212	29	No	No	No	No
73	76	10	Yes	632	36	Yes	Yes	Yes	Yes
74	69	7	No	23	37	Yes	Yes	No	Yes
75	69	8	No	11	29	No	No	No	Yes
76	66	9	No	13	29	Yes	Yes	Yes	Yes
77	60	5	Yes	14	19	No	Yes	No	Yes
78	65	1	Yes	18	34	No	No	No	Yes
79	73	1	Yes	57	60	Yes	Yes	Yes	Yes
80	69	10	Yes	55	45	No	No	No	No
81	75	14	Yes	26	27	Yes	Yes	No	Yes
82	60	6	Yes	11	27	Yes	Yes	Yes	Yes
83	61	5	Yes	10	25	No	No	No	No
84	68	4	No	8	22	Yes	No	No	No
85	63	7	Yes	63	34	No	Yes	No	Yes
86	69	3	Yes	14	58	Yes	Yes	Yes	Yes
87	64	7	Yes	26	23	Yes	No	No	No
88	78	15	No	32	36	Yes	Yes	No	Yes
89	64	5	Yes	40	62	Yes	Yes	Yes	Yes
90	65	11	Yes	16	45	Yes	Yes	No	No
91	66	16	Yes	45	18	No	No	No	No
92	63	8	No	63	44	No	Yes	No	Yes
93	74	2	Yes	18	48	Yes	Yes	Yes	Yes
94	62	8	No	28	15	Yes	No	No	No
95	73	5	Yes	36	50	Yes	No	No	Yes
96	61	17	Yes	6	18	No	Yes	No	No
97	66	12	No	50	44	No	No	No	No
98	77	6	Yes	76	25	Yes	Yes	Yes	Yes
99	64	6	Yes	44	24	Yes	Yes	Yes	Yes
100	61	10	Yes	20	46	Yes	No	No	No

101	66	8	Yes	18	22	No	Yes	No	No
102	65	5	No	42	45	No	Yes	No	No

PROFORMA

S.No:

Name: **Address:**

Age:

History:

Hesitancy	Intermittency	Incomplete emptying
Nocturia	Frequency	Dysuria
Straining	Thin stream	

Red / White urine

Others

Past History:

DM / HT/ TB/ BA/ CAD/ Previuos Surgeries

Personal history:

Smoking / Alcohol intake

Family History:

EXAMINATION:

Pallor/ Icterus/ Cyanosis/ Clubbing/ Edema/ Lymphadenopathy

PR: BP:

CVS:

RS:

P/A:

CNS: Spine / cranium

EG:

DRE: Prostate – Grade
Nodule
Tone

INVESTIGATIONS:

Urine: Albumin:
Sugar:
Deposits:
C/S:

Blood: Sugar:
Urea:
Creatinine
Hb:
ESR:
TC/DC:

Serum PSA
:

USG KUB: Kidney Right
PCS
CMD

Left.
PCS
CMD

Bladder:
Prostate: Volume
PVR:

TRUS: Prostate Volume
Hypoechoic area
Hypervascularity
Combined

Biopsy: (+/-)Hypoechoic area
Hypervascularity
Combined